Taxonomy of Organs

Introduction

The organs of immunity can be categorized as primary or secondary lymphoid organs. Primary lymphoid organs are where B cells and T cells **mature**. Secondary lymphoid organs are where B cells and T cells **activate**. This lesson touches on structure and function as well as provides some histologic background for these organs. **Primary is for maturation. Secondary is for activation.** Soldiers go to basic training (primary) and are stationed at various battle sites (secondary) once "activated" to fight.

The **primary lymphoid organs** are the **bone marrow** and the **thymus**. T and B cells are built, programmed, and trained in the primary lymphoid organs. These cells mature by first being tested by the primary lymphoid organs to make sure they work. The primary lymphoid organs also assess these cells for tolerance. This means the B cells and T cells are tested to see that they won't react to and attack self-antigens (reacting to self is autoimmunity).

The **secondary lymphoid organs** are a range of tissues existing throughout the body where immune cells commune, ready to respond to an antigen. While they vary slightly in their structure (the lymph node and the white pulp of the spleen are histologically different), they follow the same pattern of cortex-antigen-*sensing* cells and paracortex-*supervising*-T cells. This arrangement will be seen as "*darkly staining outer regions, with lightly staining inner.*" We'll explore this more in detail in this lesson. Examples include tonsils and adenoids, bronchus, **spleen**, **lymph nodes** of any location, Peyer's patches in the gut, and others such as **MALT** (mucosa-associated lymphoid tissue) or **GALT** (gut-associated lymphoid tissue).

Primary Lymphoid Organs

The **bone marrow** and its role in **B-cell maturation** is discussed in detail in #7: *B-Cell Maturation*. Suffice it to say that a **naive mature B cell** undergoes assessment for function and tolerance before it leaves the bone marrow. Bone Marrow is where B cells Mature. From the bone marrow, that mature naive B cell is sent to the secondary lymphoid organs. The histology of the bone marrow is reserved for bone pathology, in the MSK portion of the course, and so isn't discussed here in Immunology.

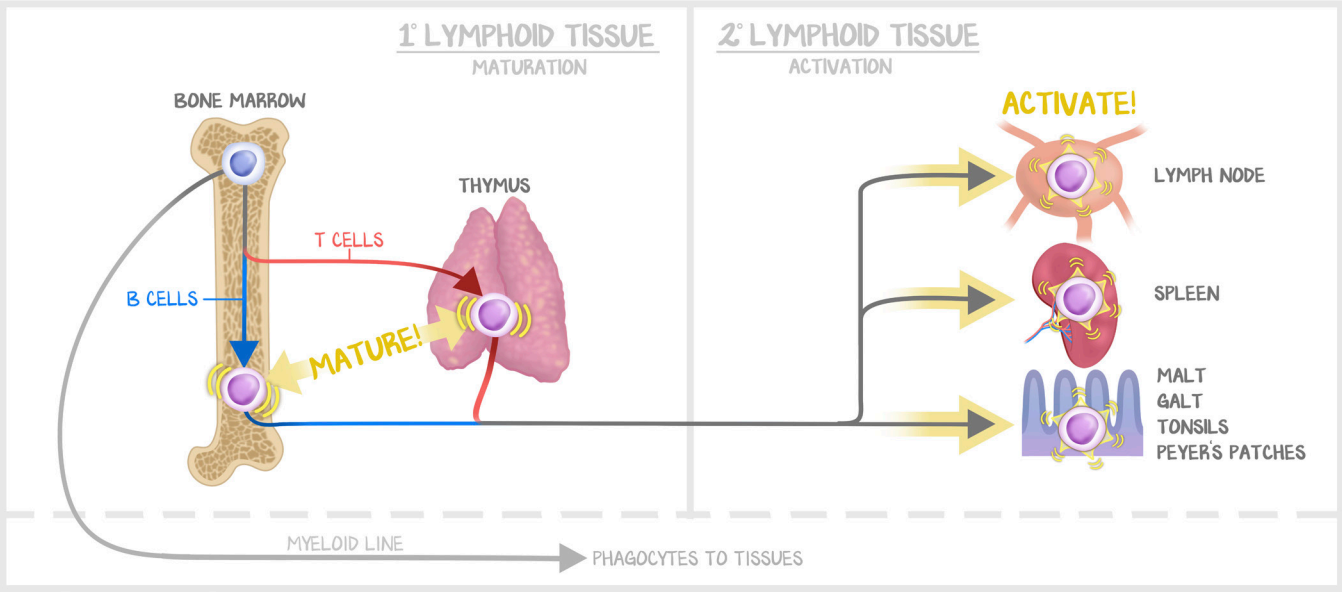


Figure 3.1: Organization of Primary Lymphoid Organs
All leukocytes are made in the bone marrow. Maturation of B cells occurs in the bone marrow. Maturation of T cells occurs in the thymus.

The **thymus** has a role in **completing T-cell maturation**. T cells, like all leukocytes, are born in the bone marrow, as clones from their original pluripotent progenitor. But very quickly the T cells are dispatched to the thymus for maturation as prothymocytes.. Almost no processing happens in the bone marrow. The thymus is a primary lymphoid organ that develops from the **third and fourth pharyngeal pouches** (epithelial in origin). The Thymus is where T cells mature. It's a foreign-antigen-free environment. It's robust during the initial maturation of the immune system (kids have big thymuses), undergoes significant atrophy in puberty, and is effectively nonexistent in adults. The thymus is bilobed, each lobe consisting of many lobules, each lobule consisting of a **cortex** and **medulla**. Each lobule is separated by septa. The cortex is **darkly staining** and the medulla is **lightly staining** and is littered with **Hassall's corpuscles.** We'll review the inner cortex, outer cortex, and medulla in #9: *T-Cell Maturation*.

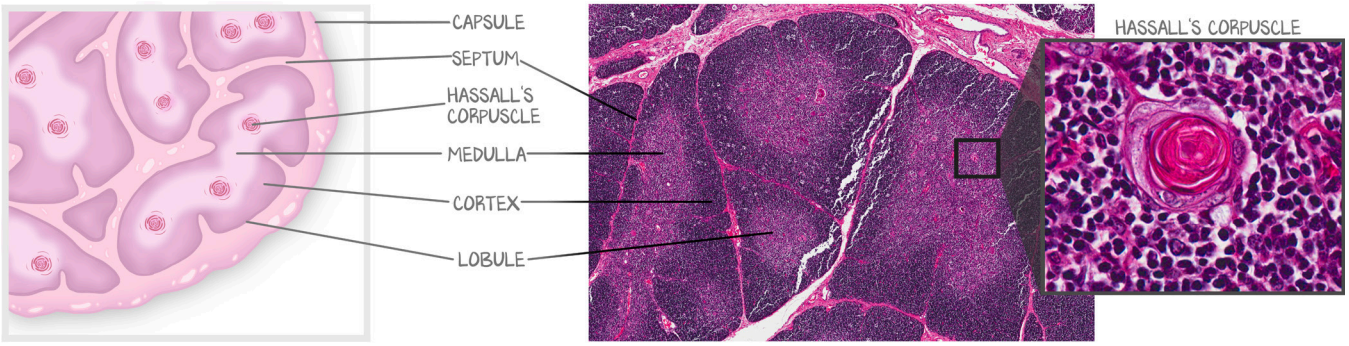


Figure 3.2: Anatomy and Histology of the Thymus
Artists rendition of the thymus showing the elements you should identify next to a histologic slide showing the cortex, medulla, septa, and highlighting Hassall's corpuscles.

Histologically, the thymus has "*darkly staining outer regions, with lightly staining inner*," and there's a risk of confusing it for a secondary lymphoid organ. Don't be fooled. The thymus has Hassall's corpuscles, while secondary lymphoid organs have a hilum. Like the thymus, germinal centers (found in lymph nodes) have "darkly staining outer regions, with lightly staining inner," but unlike the thymus, germinal centers are not separated by septa. Check out the video in the treasure chest for a review of normal lymphoid histology showcasing the PIER library's images.

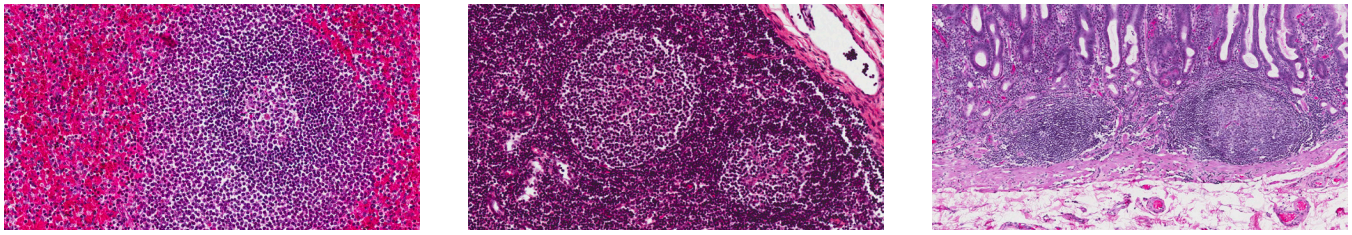
If a lymphocyte fails to mature through the primary lymphoid organ, whether because it was defective or self-reactive, that cell's genes are destroyed before it ever leaves the primary organ. This process is referred to as **clonal deletion**. After release from the primary lymphoid organs, lymphocytes go to secondary lymphoid organs. There, they are accompanied by a veteran cell. When the mature new lymphocyte thinks it's done well, it shows the supervising veteran. If the veteran approves, it delivers a costimulatory signal and the lymphocyte is deemed worthy, and lives. If the naive lymphocyte fails to receive the signal of approval, that cell is sent into quiescence. Removal of the cell line is called **clonal anergy** (for more on all this, see #14: *Mechanisms of Autoimmunity*).

Secondary Lymphoid Organs

All secondary lymphoid organs share a similar histological appearance. The idea is to have as much exposure to passing antigen as possible. The cortex is lined with B cells with their immunoglobulin receptors sticking into (and I'm trying to be general here) the flow of antigen. The **cortex** is made of **B cells** and is the **very edge** of the darkly staining areas. Just behind the B cells, in the **paracortex**, (or T cell zone) is an array of **T cells**. This region (cortex and paracortex) is so densely packed with lymphocytes that it stains intensely dark purple. The entire organ then feeds into the **medulla** in the center, which has many fewer lymphocytes than the cortex, so there are fewer nuclei to stain purple,

and therefore the medulla is much lighter in color. This setup is recycled, with some variation, in every secondary lymphoid organ: B cells in the cortex packed closely to T cells in the paracortex surrounding the lightly staining medulla. We refer to that repeating pattern as, "*darkly staining ovoid regions surrounding lightly staining things on the inside*."

All secondary lymphoid organs have **primary follicles** in their cortex. This is the ovoid structure on the slide—not-yet-activated B cells, next to a layer of T cells. When activated, the B cells proliferate, forming a **germinal center** and transforming into a **secondary follicle**. Within the germinal center there are several zones you can be asked to identify. The **dark zone** is the area of proliferation of B cells. It's dark because many cells are being born, so there's a region of densely packed nuclei. The **basal light zone** is where there's positive selection and proliferation of high-affinity immunoglobulin. Minor mutations are tolerated in the immunoglobulin gene, such that there's variability in each of the antigen-binding sites, and only the cell line with the highest affinity for the target antigen will proliferate. The **apical light zone** is where the **antibody-secreting cells** are found. The **mantle zone** is the densely packed ring of resting, nonproliferating lymphocytes outside the mantle. Only germinal centers of chronic inflammation exhibit this feature. The reason the germinal center is **lighter than the mantle zone** is because as the activated lymphocytes start making protein and proliferating, they need the space (cytoplasm) to make and store immunoglobulins for release. Proliferating lymphocytes double in size to become two identical daughters.



(a) (b) (c)

Figure 3.3: Histology of Secondary Lymphoid Tissue
With only small alterations in the overall architecture, most secondary lymphoid organs follow a repeatable pattern of primary follicles (densely packed B cells and T cells) in the outer region of the organ, and a lightly staining medulla. Germinal centers are sites of B-cell activation and proliferation. (a) The white pulp of the spleen. (b) A lymph node. (c) MALT.

Now that we have discussed the anatomy of the germinal center, let's talk a little more in depth about what the B cells are doing here and tie it in with the anatomy. Recall that we already talked about how, to become activated, T and B cells need to signal to one another that there is danger from an invading organism. Once this happens, the B cells that were out in the periphery (not in the lymphoid organs) are activated and return to "base" to communicate to the others that there is an invader. It is in the germinal center that B cells undergo proliferation (dark zone). In proliferation, the B cells undergo somatic hypermutation and selection (basal light zone). The product is high-affinity B cells that have been selected for their ability to create antibody that matches the foreign invader (like a lock and key) and can help fight the invading organism that started this whole reactionary process. The B cell can then differentiate into plasma cells (cells that produce large amounts of antibody, apical light zone) to fight the invader now, and also can differentiate into memory B cells that prepare for the next time that same invader tries to enter the body.

Lymph Nodes

Lymph nodes follow the pattern of dark staining outside, light staining inside. Additional complexities include the afferent and efferent lymphatic vessels, a capsule, and a hilum.

All lymph nodes have a **capsule** (a lining containing the organ) that is penetrated with incoming **afferent lymphatics** from the periphery. Coming from affected tissue, APCs (those return scouts) enter to show their antigen to the cells of the lymph nodes. It seems logical that most of the APCs carrying antigen would come to the lymph node nearest the infection. Proximity makes intuitive sense—they could respond quickest if they were to go from the site of infection to the nearest node. That's **NOT** how it works. Because there are infinite numbers of antigens, the APC (carrying and presenting an antigen) needs to be able to enter as many nodes as possible to find the B cell and T cell that "match" its antigen well enough to activate the B cell and T cell. Let us explain in further detail how this matchmaking process happens in the lymph node

There are many afferent lymphatics, but only one efferent lymphatic, and it exits with the vein and the artery.

The afferent lymphatic vessels bring APCs into the lymph node to try to find and activate B and T cells. The T and B cells come into the node through arteries and enter the lymphatic tissue by squeezing through a **high endothelial venule** (HEV). That is a venule with a special name, the vessel-just-larger-than-a-capillary on the venous side. While they are in the tissue, they have a chance to mingle with the APCs that have brought foreign invaders, and if they find a match, they can respond through a complex activation process. If the T and B cells are not activated, they leave the node through efferent lymphatic vessel and NOT through blood vessels.

Think of it as a city with multiple highways entering and exiting. The APCs enter the city from one highway (afferent lymphatics) and the other cells (for example, B cells) come from the other direction on another highway (artery and then the HEV). Once they are in the city (cortex of the node), as they pass each other they slow down enough to decide whether they should stop. If not, the T cells, B cells and APCs leave through yet another highway (efferent lymphatic). Those that enter from the afferent lymphatics naturally descend to the efferent. Those cells that enter through HEVs follow the same path, heading up into the cortex and back down through the medulla through the same efferent lymphatic. There are many afferent lymphatics, but only one efferent lymphatic, and it exits the hilum along with the vein and the artery. The **hilum** is where the blood vessels are. Blood flows in from the artery and leaves through the vein. Filtration of blood occurs at the capillaries within the medulla, so **memory cells** and **plasma cells** will be stationed closest to the blood vessels. There they both sense for antigens in the HEVs and can release antibodies into the vein.

This means that any leukocyte that gets into the lymphatics will exit through the lymphatics. The cells can then enter the next node in the chain. Eventually, the lymph comes together and exits near the heart where the APCs, B cells, and T cells can be recirculated and continue a random distribution throughout the body in an attempt to find a foreign invader.

Don't worry: if the APC didn't find its B or T cell match, it has many chances! Leukocytes circulate in blood. Antibodies circulate in blood. There are near infinite permutations of antigens and antigen receptors. Rather than trying to have all of the antigen recognition in every node, we need only one of each antigen recognizer in the BODY. APCs may come from the arm, and go through the lymph node of the arm, but lymph drains into systemic venous circulation. All the blood comes to the heart. All APCs come to the heart. Then the heart blasts them out into the periphery again to repeat the process. This maximizes the APC exposure to many antigen-recognizing cells, maximizing the chance that the antigen being carried by the APC will encounter the antigen-recognizer.

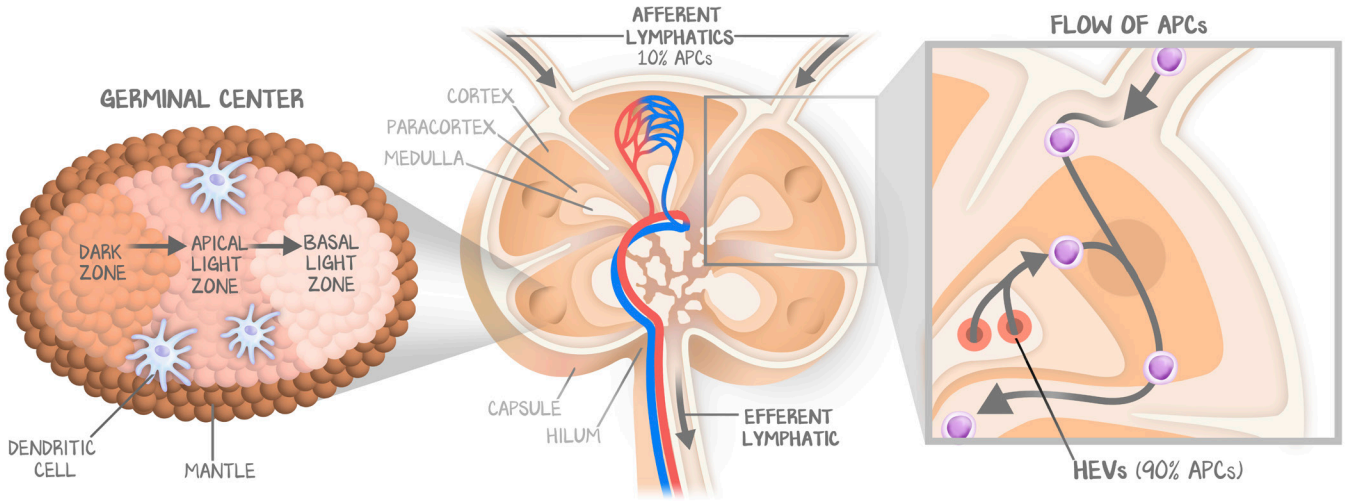
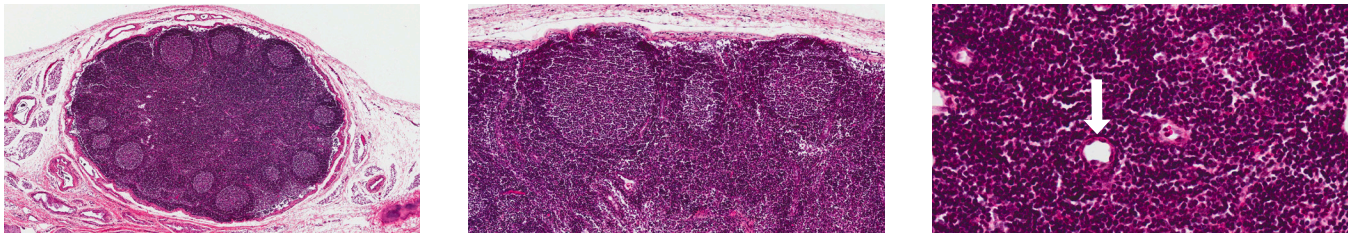


Figure 3.4: Lymph Nodes
Artist's rendition of a lymph node. The node is encapsulated, blood vessels entering and exiting through the hilum. There are three regions; the cortex lines the lymphatics, which is where circulating lymphocytes exit into the node via high endothelial venules.



(a) **(b)** **(c)**

Figure 3.5: Lymph Nodes
(a) Low magnification of a lymph node. (b) Moderate zoom showing multiple germinal centers. (c) High endothelial venule.

The cortex has B cells; the paracortex has T cells. There are also primary follicles and secondary follicles with germinal centers, just as was described in the last section.

Spleen

The spleen is complex because it has two functions—hematologic and immunologic. Handling these functions are the "red pulp" and "white pulp," respectively. These are known as "regions," although they are not spatially distinct from one another. In fact, "red pulp" is not red and "white pulp" is not white—they were named based on their **function and NOT what they look like**. Since red blood cells are hematologic, the hematologic function of the spleen was named "red pulp." Since white blood cells are immunologic, the immunologic function of the spleen was named "white pulp."

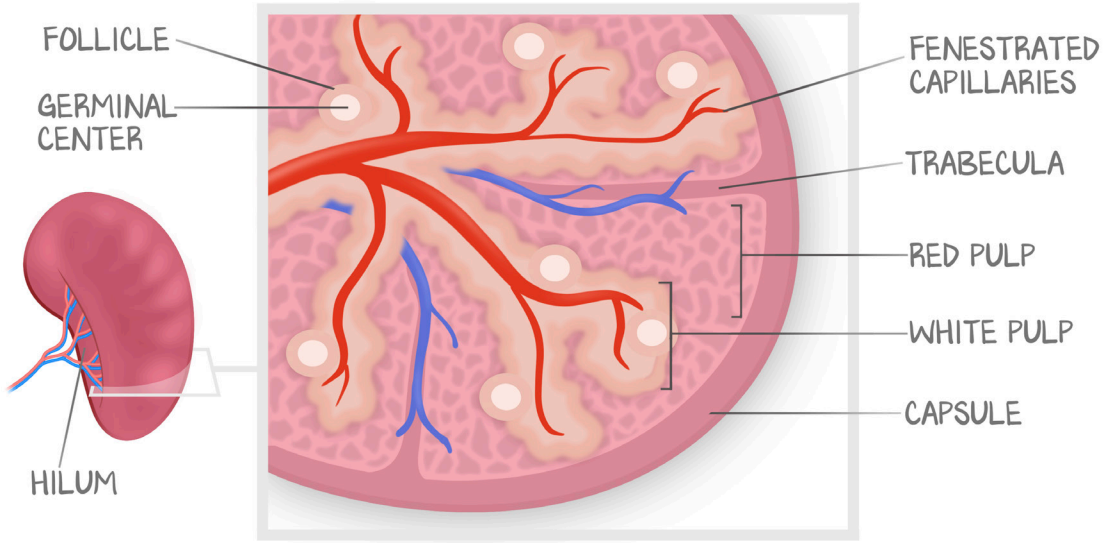
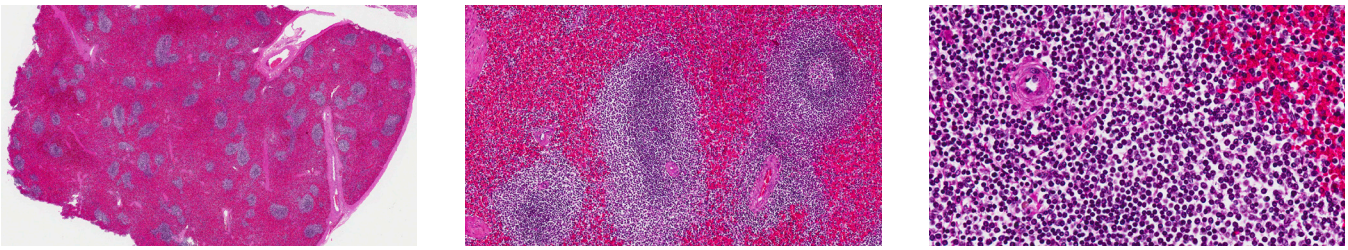


Figure 3.6: The Spleen
Artist's rendition of the spleen.



(a) **(b)** **(0c)**

Figure 3.7: The Spleen
(a) Low magnification showing the patchy nature of red pulp (which is red with RBCs) dispersed amongst patches of lymphocytes forming germinal centers. (b) Moderate zoom showing a germinal center. (c) High-power magnification. This specialized stain highlights RBCs. In our image, red pulp is red.

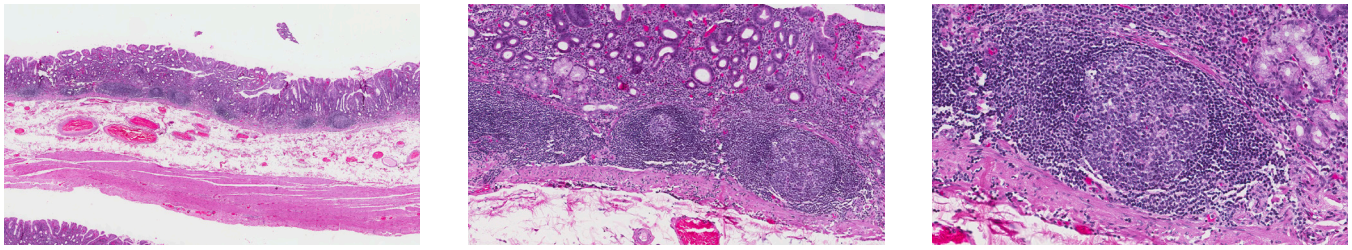
Similar to the lymph node, with its clusters of cortex-paracortex-medulla all next to each other, when looking at the spleen on microscope you can detect distinct units that resemble every other secondary lymphoid organ—clusters of darkly staining primary follicles in the cortex packed with lymphocytes surrounding the sparsely populated and lighter staining medulla. The spleen also has a **capsule** like a lymph node, and has a **hilum**. The big difference between the spleen and a lymph node is that the **spleen doesn't have lymphatics** and **doesn't have high endothelial venules** (it has **sinusoidal capillaries** instead).

The **immunologic** (**white pulp** for white cell, immune function) function of the spleen is just like a lymph node. In a lymph node, antigen comes in, crosses T cells in the paracortex, then T cells activate B-cell follicles to form germinal centers. APCs enter the lymph node via arteries, gain access to T cells through high endothelial venules, then leave through the efferent lymphatic. In the spleen, the APCs get to the white pulp via arterioles, which enter through the **fenestrated capillaries** (the spleen's white-pulp high endothelial venule equivalent). These white-pulp arterioles are surrounded by T cells, which act like the paracortex of the lymph node. T cells see the antigen, then they activate B cells within the follicles of the white pulp.

The spleen just makes it complicated because it ALSO has a separate hematologic function that makes a slice of it look not like a node. The white pulp is doing the node stuff, and that structure is interspersed with red pulp, doing its own thing. The **hematologic** (**red pulp** for red cells, heme) function of the spleen is to act as a **macromolecular antigen filter**. The splenic venules are deeply fenestrated. The holes are big. Lots can get through. Most things are supposed to get through. But should something **not be able to get through the venule**, it gets stuck. And the spleen, identifying that thing as stuck, knows that it's not supposed to be there, so it dispatches macrophages to destroy it. The largest, deepest function is the removal of old, dying, or damaged red cells.

Others

If you haven't noticed the common theme: a central lightly staining area surrounded by a dense ring of darkly staining areas. This was true of white pulp, lymph nodes, and even the thymus. Mucosal-associated lymphoid tissue (MALT) such as palatine tonsils, lingual tonsils, and pharyngeal tonsils (adenoids), and Peyer's patches have similar features. Gut-associated lymphoid tissue (GALT) is the same thing, only in the gut.



(a) (b) (c)

Figure 3.8: GALT
(a) Low magnification. (b) Moderate magnification. (c) High magnification with a visible dark zone, light zone, and marginal zone.

Citations

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